Food Sci. Biotechnol. Vol. 14, No. 4, pp. 509 ~ 513 (2005)

Food Science and Biotechnology

Change of Ginsenoside Composition in Ginseng Extract by Vinegar Process

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Abstract The purpose of this study was to develop a new preparation process of ginseng extract using high concentrations of ginsenoside Rg_3, a special component in red ginseng. From when the ginseng saponin glycosides transformed into the prosapogenins chemically, they were analyzed using the HPLC method. The ginseng and ginseng extract were processed with several treatment conditions of an edible brewing vinegar. The results indicated that ginsenoside Rg_3 quantities increased over 4% at the pH 2-4 level of vinegar treatment. This occurred at temperatures above 90°C, but not occurred at other pH and temperature condition. In addition, the ginseng and ginseng extract were processed with the twice-brewed vinegar (about 14% acidity). This produced about 1.5 times more ginsenoside Rg_3 than those processed with regular amounts of brewing vinegar (about 7% acidity) and persimmon vinegar (about 3% acidity). Though the white ginseng extract was processed with the brewing vinegar over four hr, there was no change for ginsenoside Rg_3. However, the VG8-7 was the highest amount of ginsenoside Rg_3 (4.71%) in the white ginseng extract, which was processed with the twice-brewed vinegar for nine hr. These results indicate that ginseng treated with vinegar had 10 times the quantity of ginsenoside Rg_3, compared to the amount of ginsenoside Rg_3 in the generally commercial red ginseng, while ginsenoside Rg_3 was not found in raw and white ginseng.

Keywords: ginseng, brewing vinegar, ginseng saponin, prosapogenin, ginsenoside Rg_3

Introduction

Korean ginseng (*Panax ginseng*) is listed as a medicinal herb in the reputable article of *Shennong Benaojing*, the representative Chinese herbal dictionary. As a special medicinal herb, Korean ginseng has a sweet taste, warms up the body slightly, and is known to be effective in maintaining the health of the lungs and spleen (1). Korean ginseng contains more than 30 different ginseng saponins, which produce various physiological activities (2, 3). These include polyacetylenes, which are known to produce anti-tumor activities on various cancers (4); phenolic compounds produce antioxidant activities (5), proteins, which produce radio-protective activities on victims of nuclear attacks (6), and acidic polysaccharides, which have immune controlling activities in various tests using mouse experimental model (7).

Ginsenosides, or ginseng saponin as it's called, is known as the main pharmacological component of Korean ginseng. The Shibata Group of Tokyo University has identified the chemical structure of ginsenoside (8). Ginsenosides are classified in two groups: protopanaxadiols and protopanaxatriols. The main component of the protopanaxadiols is ginsenoside Rb_1, which suppresses the overall activity of the central nervous system (CNS). The main component of the protopanaxatriols is ginsenoside Rg_1, which stimulates the CNS and is important component for explanation of adaptogen activity theory of Korean ginseng.

Red ginseng (Ginseng Radix rubra) refers to the steam-dried ginseng, while white ginseng (Ginseng Radix alba) refers to natural-dried ginseng. The ginseng was first dried under sunlight after being skinned and the removal of very fine roots called fine ginseng root (Ginseng Radix palba).

Ginsenoside Rg_3 is not found in raw and white ginseng, but it located in red ginseng, which contains a small amount of ginsenoside Rg_3 generated during the steam-dried process. Ginsenosides Rg_3 were found to have produced anticancer activity on phorbol ester-induced cyclooxygenase-2 expression, NF-kappaB activation and tumor promotion (9). Rg_3 also lowered blood pressure by endothelium-dependant relaxation in response to ginsenosides in rat aorta (10). Rg_3 in methanol extract of heat-processed ginseng provided antioxidant and anti-tumor promoting activities (11). But the steam-dried process to prepare red ginseng is expensive and has a low Rg_3 yield. Therefore, to produce more specialized and functionalized ginseng preparation with high concentrations of special components such as Rg_3, it is essential to develop a lower priced yet more efficient ginseng preparation process. For this reason, many attempts have been made recently to produce a ginseng preparation having high concentrations of ginsenoside Rg_3.

According to Shibata's 1966 report (8), by hydrolyzing saponin with a weak acid such as acetic acid, the C-20 of glucoside bond (ginsenosides Rb_1, Rb_2, Rc, and Rd) is hydrolyzed and only prosapogenin [20(R & S)-ginsenoside Rg_3] is obtained. However, this process produced only a very small pure standard substance. Meanwhile, to produce a ginseng preparation with high concentrations of

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Received March 24, 2005; accepted July 14, 2005

ginsenoside Rg_3, some researchers have studied the physical process method at high temperatures (12) or/and the biochemical process using enzymes.

Although this method can produce some quantity of ginsenoside Rg_3, it requires a long manufacturing phase and specially designed equipment such as high-pressure heaters. Additional risks in the manufacturing process are created, especially with the necessity for higher temperatures using this method. For instance, the ginseng preparation could be charred in the mass manufacturing process using this method.

Therefore, the purpose of this study was to investigate the chemical transformation of ginseng saponin glycosides to ginsenoside Rg_3 by the hydrolyzing process with various vinegars.

Materials and Methods

Materials The white ginseng (Ginseng Radix alba) used in the experiment was purchased in August, 2001 in Geumsan, Republic of Korea. The various edible brewing vinegars, twice-brewed vinegar (about 14% acidity), brewing vinegar (about 7% acidity), and persimmon vinegar (about 3% acidity), were purchased in Seoul, Republic of Korea. The acetonitrile and distilled water for HPLC were purchased from J. T. Baker SOLUSORB (New Jersey, USA). Other chemicals for experiment were analytical reagent grade. The standard material of ginsenosides from *Panax ginseng* was prepared as previously described (13, 14) and its purity was over 99% according to the mass spectrum and ^{13}C-NMR spectroscopy.

Preparation of white ginseng extracts A precise amount (500g) of ginseng fine powder (white ginseng and fine ginseng root) was extracted four times using 2,500 mL of 95% ethyl alcohol over four hr. The mixture was refluxed during the second hr. at temperatures of 80-90°C. After cooling, the filtered solution was completely concentrated by vacuum evaporation.

Preparation of fine ginseng root processed with the brewing vinegar The VG1-1 and VG1-2 samples were prepared as follows; an amount of 10 volumes of brewing vinegar (pH 2.90) were added to 50 g of fine ginseng root, and extracted once at 100°C for two hr (VG1-1) and 24 hr (VG1-2). The remaining solution was concentrated by vacuum evaporation and freeze-dried to obtain a brownish extract.

Preparation of white ginseng extracts processed with various brewing vinegars and other organic acids The VG2-1 sample was prepared as follows: 8 volumes of brewing vinegar (pH 2.47) were added to 10 g of white ginseng extract, then reacted at 90°C for three hr. Then, the sample was filtered and vacuum dried to obtain a brownish extract. The extract was analyzed using the HPLC method. The preparation conditions of all samples are described in Table 1.

HPLC analysis 10 mg of ginseng and vinegar ginseng extracts were each dissolved with 1 mL of 40% acetonitrile for HPLC analysis (13, 14). In order to obtain standard curves for quantifying ginsenosides (Rb_1, Rb_2, Rc, Rd, Re, Rf, Rg_1, Rg3 and s-Rh_1), 1 mg of each standard ginsenoside was dissolved with 1 mL of methanol. The relative standard deviation for triplicate injections was less than 1.0%. The area value of each ginsenoside in 250, 500 and 1000 ppm was used to measure curves.

Table 1. The processing conditions of various brewing vinegars and organic acids on the white ginseng extracts

Samples	Treatment material	Temperature (°C)	Time (hr)
VG2-1	brewing vinegar (pH 2.47)	90	3
VG2-2	persimmon vinegar (pH 3.45)	90	3
VG3-1	citric acid solution (pH 5.02)	90	3
VG3-2	glacial acetic acid (pH 0.27)	90	3
VG4-1	persimmon vinegar (pH 3.45)	90	6
VG4-2	persimmon vinegar (pH 3.45)	120	6
VG4-3	brewing vinegar (pH 2.47)	90	6
VG4-4	persimmon vinegar (pH 3.45)	60	6
VG4-5	citric acid solution (pH 5.02)	60	6
VG4-6	glacial acetic acid (pH 0.27)	60	6
VG4-7	citric acid solution (pH 5.02)	90	6
VG4-8	glacial acetic acid (pH 0.27)	90	6
VG4-9	citric acid solution (pH 5.02)	120	6
VG4-10	glacial acetic acid (pH 0.27)	120	6
VG5-1	twice brewing vinegar (pH 2.30)	90	3
VG5-2	twice brewing vinegar (pH 2.30)	90	6
VG5-3	twice brewing vinegar (pH 2.30)	90	9
VG6-1	brewing vinegar (pH 2.47)	90	3
VG6-2	brewing vinegar (pH 2.47)	90	6
VG6-3	brewing vinegar (pH 2.47)	90	9
VG7-1	persimmon vinegar (pH 3.45)	90	3
VG7-2	persimmon vinegar (pH 3.45)	90	6
VG7-3	persimmon vinegar (pH 3.45)	90	9
VG8-1	twice brewing vinegar (pH 2.30)	90	3
VG8-2	twice brewing vinegar (pH 2.30)	90	4
VG8-3	twice brewing vinegar (pH 2.30)	90	5
VG8-4	twice brewing vinegar (pH 2.30)	90	6
VG8-5	twice brewing vinegar (pH 2.30)	90	7
VG8-6	twice brewing vinegar (pH 2.30)	90	8
VG8-7	twice brewing vinegar (pH 2.30)	90	9
VG8-8	twice brewing vinegar (pH 2.30)	90	10
VG8-9	twice brewing vinegar (pH 2.30)	90	11
VG8-10	twice brewing vinegar (pH 2.30)	90	12

Results and Discussion

As shown in Table 2, ginsenoside composition of fine ginseng root extract (GRP), VG1-1 and VG1-2 preparations were analyzed using the HPLC method (13, 14). A typical HPLC chromatogram of ginsenosides detected from the vinegar processed ginseng is indicated in Fig. 3. Ginsenoside Rg_3, a special component in red ginseng shown in Fig. 1, was not detected at all in the fine ginseng root extract. However, a high amount of ginsenoside Rg_3 was detected in VG1-1 and VG1-2 preparations.

Table 2. The composition of ginsenoside in the fine ginseng roots processed with brewing vinegar

Samples	Ginsenosides (%)								
	Rb_1	Rb_2	Rc	Rd	Re	Rf	Rg_1	Rh_1	Rg_3
GRP[1]	1.850±0.007	0.595±0.004	1.124±0.005	0.488±0.002	0.557±0.029	0.099±0.007	0.142±0.003	0.799±0.007	0±0
VG1-1[2]	0.043±0.002[a]	0.058±0.002[a]	0.218±0.008[a]	0.108±0.006[a]	0.020±0.0006[b]	0.138±0.002[c]	0.013±0.001[a]	1.253±0.005[a]	1.4760.006[a]
VG1-2[3]	0±0[a]	0±0[a]	0±0[a]	0.019±0.001[a]	0.014±0.001[b]	0.009±0.0004[b]	0±0[a]	0.505±0.004[a]	0.558±0.009[a]

[1]GRP: dried fine ginseng root extract.
[2]VG1-1: dried fine ginseng-root processed with brewing vinegar for 2 hr.
[3]VG1-2: dried fine ginseng-root processed with brewing vinegar for 24 hr
Values represent the mean±S.E. (n=3)
[a]$p<0.001$ vs. GRP, [b]$p<0.01$ vs. GRP, [c]$p<0.05$ vs. GRP.

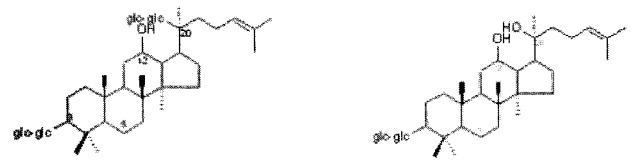

Fig. 1. Transformation of protopanaxadiol saponin ginsenoside Rb_1 to ginsenoside Rg_3.

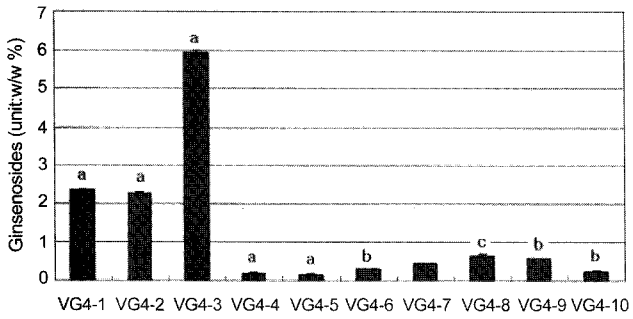

Fig. 2. Ginsenoside Rg_3 content of the white ginseng extracts processed with various brewing vinegars and organic acids by the temperatures. VG4-1: persimmon vinegar at 90°C, VG4-2: persimmon vinegar at 120°C, VG4-3: brewing vinegar at 90°C, VG4-4: persimmon vinegar at 60°C, VG4-5: citric acid solution at 60°C, VG4-6: glacial acetic acid at 60°C, VG4-7: citric acid solution at 90°C, VG4-8: glacial acetic acid at 90°C, VG4-9: citric acid solution at 120°C, VG4-10: glacial acetic acid at 120°C. Values represent the mean±S.E. (n=3). [a]$p<0.001$ vs. VG4-7, [b]$p<0.01$ vs. VG4-7, [c]$p<0.05$ vs. VG4-7.

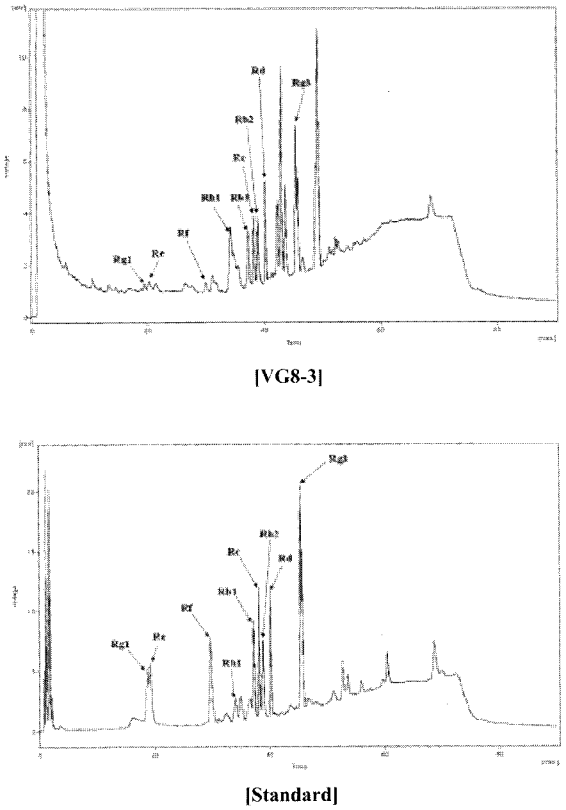

Fig. 3. HPLC chromatogram of ginsenosides detected from the vinegar processed ginseng, VG8-3 and compared with chromatogram of ginsenoside standards.

Particularly, VG1-1 preparation had the highest content of ginsenoside Rg_3 at 1.477%, which corresponded with 44.39% of the total amount of saponin. Also, the VG1-2 preparation had a ginsenoside Rg_3 content rating of 0.557%, which corresponded to 50.45% of the total saponin amount.

Contents of ginsenoside Rg_3 for the above pH 4 (VG3-1) or below pH 2 (VG3-2) were 0.26% and 0.59%, respectively. Ginsenoside Rg_3 contents of VG2-1 and VG2-2 preparations (in the range between pH 2 and pH 4) were significantly increased to 1.93% and 1.27%, respectively (see in Table 3). It was speculated that the strong acidity of glacial acetic acid may prevent the generation of ginsenoside Rg_3, since the total amounts of saponin in VG3-2 were significantly lower than those of other samples.

As shown in Fig. 2, when the vinegar process was performed at temperatures below 70°C, the contents of ginsenoside Rg_3 for VG4-4, VG4-5, and VG4-6 preparations were at 0.19%, 0.17%, and 0.31%, respectively.

However, when the vinegar process was performed at temperatures above 90°C (VG4-1, VG4-2 and VG4-3), the contents of ginsenoside Rg_3 were increased. When the levels ranged from pH 2 to 4, there was no significant difference in the contents of ginsenoside Rg_3 at temperatures of 90°C and 120°C. However, for the levels above pH 4, the contents of ginsenoside Rg_3 increased with the temperature. This implies that temperature is a significant factor in the generation of ginsenoside Rg_3 below a certain level of acidity.

To produce higher amounts of ginsenoside Rg_3, white ginseng extract was prepared for vinegar processing instead of ginseng root. Also, to find out optimal production conditions for ginsenoside Rg_3, various vinegars including the twice-brewed vinegar, brewing vinegar, and persimmon vinegar, were used.

Table 3. The composition of ginsenoside in the white ginseng extracts processed with various brewing vinegars and organic acids

Samples	Ginsenosides (%)								
	Rb_1	Rb_2	Rc	Rd	Re	Rf	Rg_1	Rh_1	Rg_3
VG2-1[1)]	0.360±0.124[b]	0.327±0.085[b]	0.283±0.042[b]	0.743±0.058[b]	0.027±0.007[b]	0.137±0.009	0.077±0.003	0.840±0.105	2.763±0.173[b]
VG2-2[2)]	0.640±0.093[c]	0.553±0.103[c]	0.510±0.096[c]	0.960±0.080[c]	0.127±0.049[b]	0.127±0.019[c]	0.097±0.024	0.830±0.181	2.363±0.100[a]
VG3-1[3)]	1.850±0.196	1.887±0.207	1.603±0.154	1.670±0.078	1.870±0.139	0.180±0.021	0.570±0.135	0.550±0.025	0.280±0.031
VG3-2[4)]	0±0[c]	0±0[c]	0±0[b]	0±0[b]	0.070±0.006[b]	0±0[c]	0.057±0.003	0.207±0.012[b]	0.333±0.134

[1)]VG2-1: white ginseng extract processed with brewing vinegar.
[2)]VG2-2: white ginseng extract processed with persimmon vinegar.
[3)]VG3-1: white ginseng extract processed with citric acid solution.
[4)]VG3-2: white ginseng extract processed with glacial acetic acid.
Values represent the mean±S.E. (n=3)
[a]$p<0.001$ vs. VG3-1, [b]$p<0.01$ vs. VG3-1, [c]$p<0.05$ vs. VG3-1.

Table 4. The composition of ginsenoside in the white ginseng extracts processed with various brewing vinegars as time passes

Ginsenosides	GRA[1)]	Twice brewing vinegar			Brewing vinegar			Persimmon vinegar		
		3 h (VG5-1)	6 h (VG5-2)	9 h (VG5-3)	3 h (VG6-1)	6 h (VG6-2)	9 h (VG6-3)	3 h (VG7-1)	6 h (VG7-2)	9 h (VG7-3)
Rb_1 (%)	2.257±0.03	0.980±0.98[a]	0.455±0.005[a]	0.200±0.01[a]	1.550±0.03[a]	1.100±0.02[a]	0.825±0.015[a]	1.690±0.01[a]	1.475±0.005[a]	0.710±0.53[c]
Rb_2 (%)	2.547±0.02	1.010±0.005[a]	0.465±0.005[a]	0.200±0.01[a]	1.610±0[a]	1.310±0.16[b]	0.860±0.02[a]	1.790±0.06[a]	1.525±0.005[a]	1.280±0.04[a]
Rc (%)	2.073±0.02	0.690±0.01[a]	0.335±0.025[a]	0.275±0.005[a]	1.090±0.005[a]	0.805±0.025[b]	0.630±0.02[a]	1.180±0.01[a]	1.065±0.005[a]	0.890±0[a]
Rd (%)	1.960±0.03	1.310±0.03[a]	0.900±0.02[a]	0.420±0.02[a]	1.690±0.01[b]	1.360±0.13[b]	1.305±0.095[b]	1.760±0.025[c]	1.695±0.015[b]	1.540±0.05[b]
Re (%)	2.920±0.07	0.560±0.02[a]	0.130±0[a]	0.050±0[a]	1.290±0.01	0.600±0.01[b]	0.270±0.02[a]	1.970±0.045[b]	0.605±0.505[b]	0.550±0.01[a]
Rf (%)	0.237±0.03	0.210±0.005	0.140±0.01	0.125±0.005[c]	0.190±0.01	0.165±0.005	0.160±0.01	0.190±0.005	0.180±0	0.170±0.01
Rg_1 (%)	1.227±0.06	0.220±0.01[a]	0.035±0.035[a]	0.015±0.015[a]	0.510±0.01[b]	0.130±0.01[a]	0.065±0.015[a]	0.700±0.025[b]	0.380±0.02[b]	0.260±0.02[a]
Rh (%)	0.203±0.01	1.150±0.02[a]	1.120±0.03[a]	1.105±0.075[a]	1.070±0.01[a]	1.255±0.025[a]	1.315±0.085[a]	0.860±0.02[a]	1.105±0.005[b]	1.180±0.03[a]
Rg_3 (%)	0.200±0.03	2.230±0.02[a]	3.405±0.025[a]	3.745±0.015[a]	1.280±0.025[a]	2.090±0.01[a]	2.615±0.095[a]	0.840±0.025[a]	1.350±0[a]	1.685±0.005[a]

[1)]GRA: white ginseng extract. [abc]
Values represent the mean±S.E. (n=3)
[a]$p<0.001$ vs. GRA, [b]$p<0.01$ vs. GRA, [c]$p<0.05$ vs. GRA.

Table 5. Ginsenoside composition of the white ginseng extracts processed with twice brewing vinegar as time passes

Ginsenosides	GRA[1)]	3 h (VG8-1)	4 h (VG8-2)	5 h (VG8-3)	6 h (VG8-4)	7 h (VG8-5)	8 h (VG8-6)	9 h (VG8-7)	10 h (VG8-8)	11 h (VG8-9)	12 h (VG8-10)
Rb_1 (%)	2.257±0.03	0.670±0.104[b]	0.457±0.087[b]	0.277±0.062[b]	0.187±0.047[a]	0.097±0.048[a]	0.073±0.023[a]	0.050±0.02[a]	0.023±0.009[a]	0.023±0.009[a]	0.023±0.009[a]
Rb_2 (%)	2.547±0.02	0.723±0.098[b]	0.503±0.079[b]	0.313±0.064[a]	0.217±0.043[a]	0.120±0.047	0.097±0.022[a]	0.070±0.02[a]	0.047±0.012[a]	0.047±0.012[a]	0.040±0.01[a]
Rc (%)	2.073±0.02	0.857±0.078[b]	0.703±0.06[b]	0.557±0.032[a]	0.493±0.023[a]	0.423±0.034[a]	0.420±0.015[a]	0.387±0.007[a]	0.377±0.013[a]	0.353±0.007[a]	0.350±0.015[a]
Rd (%)	1.960±0.03	1.040±0.107[c]	0.843±0.094[b]	0.627±0.073[b]	0.507±0.071[b]	0.343±0.103[b]	0.320±0.06[b]	0.247±0.057[a]	0.173±0.028[a]	0.163±0.044[b]	0.140±0.05[a]
Re (%)	2.920±0.07	0.417±0.114[b]	0.227±0.057[b]	0.123±0.028[a]	0.100±0.01[a]	0.070±0.012[a]	0.080±0.006[a]	0.073±0.003[a]	0.067±0.003[a]	0.070±0.001[a]	0.063±0.009[a]
Rf (%)	0.237±0.03	0.267±0.102	0.160±0.006	0.147±0.003	0.133±0.007	0.120±0.01	0.128±0.003	0.113±0.003	0.103±0.003[c]	0.107±0.009	0.103±0.009
Rg_1 (%)	1.227±0.06	0.090±0.015[b]	0.050±0.01[b]	0.033±0.003[b]	0.030±0[b]	0.027±0.003[b]	0.030±0[b]	0.030±0[b]	0.030±0[b]	0.030±0[b]	0.030±0[b]
Rh_1 (%)	0.203±0.01	1.440±0.067[b]	1.273±0.11[c]	1.347±0.028[a]	1.293±0.047[b]	1.113±0.007[a]	1.197±0.041[b]	1.060±0.035[a]	0.990±0.068[c]	1.077±0.052[b]	0.947±0.042[a]
Rg_3 (%)	0.200±0.03	3.627±0.185[b]	4.157±0.148[a]	4.173±0.127[a]	4.303±0.182[a]	4.403±0.139[a]	4.49±0.035[a]	4.447±0.099[a]	4.303±0.058[a]	4.533±0.109[a]	4.44±0.064

[1)]GRA: white ginseng extract.
Values represent the mean±S.E. (n=3)
[a]$p<0.001$ vs. GRA, [b]$p<0.01$ vs. GRA, [c]$p<0.05$ vs. GRA.

As shown in Table 4, the ginsenoside Rg_3 content from processed white ginseng extract with the twice-brewed vinegar, was higher than those of processed white ginseng extract with brewed and persimmon vinegar. Also, the results show that the contents of ginsenoside Rg_3 were continuously increased when the white ginseng extract was processed with the twice-brewed vinegar for nine hr. As shown in Table 5, the ginsenoside Rg_3 content of processed white ginseng extract with twice-brewed vinegar over four hr kept over 4%.

Hence, the optimal vinegar process condition to produce more ginsenoside Rg_3 content from white ginseng extract, involves the appropriate amount of vinegar acidity (pH), with a process time of 0.5 to 24 hr, and temperature ranging from 70°C to 150°C.

Conclusively, ginsenoside Rg_3 content from processed white ginseng extract with vinegar was over 10 times with that of ginsenoside Rg_3 in the red ginseng. Further studies comparing the physiological activities between glycoside form (Rb_1) and prosapogenin form (Rg_3) will be performed in the near future.

Acknowledgments

This work was supported by Korea Research Foundation Grant (KRF-2001-005-F00013).

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